UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 0 3 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Petition for Tolerances for Sulfosate (Touchdown®; EPA reg. 10182-276) in/on Soybean Seed, Forage, and Hay and Amended Registration for Touchdown® 4LCE (EPA REg. No. 10182-277).

Tox. Chem. No. 893C
PD No. 128501
Project No. 1-0110
ID No. 0F03860
Submission No. S287955
DP Barcode No. D157626

TO: R.Taylor/C.Giles, PM Team # 25
Registration Division (H7505C)

FROM: Nguyen B. Thoa, Ph.D. NBT 07/27/92
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head Pamela M. Hurley 7/29/92 KB 8/3/92
Section I, Toxicology Branch I
Health Effects Division (H7509C)

I. Actions Requested:

ICI Americas, Inc., Agricultural Products, Wilmington, Delaware, has submitted a Petition for tolerances for Sulfosate in/on the raw agricultural commodities soybean seed at 2.0 ppm, soybean forage at 1.0 ppm, and soybean hay at 3.0 ppm. The proposed tolerance levels are for the combined residues of Sulfosate (Trimethylsulfonium carboxymethylaminomethylphosphonate) and its metabolite aminomethylphosphonic acid (AMPA) in or on the above mentioned commodities, resulting from the use of Touchdown® concentrate and the formulation Touchdown® 4LCE (EPA reg. No. 10182-277.

The Petitioner has also applied for an amended registration for the formulation Touchdown® 4LCE to add the use on soybeans.

II. Conclusions:

A. The Toxicological Data Base on Sulfosate is incomplete and Toxicology Branch (TB) cannot act favorably on the requested tolerances and amended registration. The following are data gaps:

1. Acute delayed Neurotoxicity/hen (81-7a): Sulfosate is a salt with a 1:1 molar ratio of a tertiary sulfur cation (trimethylsulfonium) and a phosphonate anion (carboxymethylaminomethylphosphonate).

2. Acute Neurotoxicity/mammals (81-7b): This test will be required to support the registration of pesticides in the near future. It is presently required for sulfosate because this compound has demonstrated general neurotoxic symptoms in acute oral, dermal, and inhalation toxicity studies.

3. 90-Day Neurotoxicity/mammals (82-5b): Sulfosate has demonstrated neurotoxicity in acute oral, dermal and inhalation toxicity studies.

4. Acute Inhalation toxicity study (81-3) with Touchdown 4LCE.

5. In addition, TB will require a 28-Day Neurotoxicity/hen (82-5a) if the acute delayed Neurotoxicity/hen is positive.

B. Sulfosate needs to be submitted to the HED RfD Mini Peer Review, for an RfD evaluation and toxicological assessments of its potential for inducing oncogenicity, developmental and neurotoxicity, before tolerances can be established.

C. Two formulations, Touchdown 4LC and 4LCE are included in the HED Tox one-liners. According to the data submitted in the Petition Package (Product chemistry: Section A; a.i. content: Section B; acute toxicity studies: Section C), the formulation involved in this petition is Touchdown 4LCE.

III. Background:

Sulfosate is a nonselective foliar systemic herbicide used to control a broad spectrum of emerged weeds. The proposed use is for the control of weeds in soybean fields.

Touchdown® concentrate is the technical grade (52.2% a.i.; 5.5 lbs. a.i./gallon). Touchdown® 4LCE is a formulation containing 39.9% a.i. (4 lbs. a.i./gallon) and 60.1% inert ingredients which use were cleared by the Agency.

The petitioner proposes an application by broadcast (no air application) to actively growing weeds before soybean planting plus a spot spray or wiper application after soybean planting

2

but before crop emergence, at a maximun rate of 4 lbs. a.i./acre/year. "In the event of failure, only soybean or corn can be replanted within 40 days of application.

Based on the results from 13 residue field trials conducted in 11 States nationwide, application of Touchdown® concentrate and Touchdown® 4LCE by pre- or postemergence broadcast at 8 lbs. a.i./A, plus spot treatment at 2 lbs. a.i./A 8 weeks prior to harvest, will not result in Sulfosate residues in/on soybean seeds, forage, and hay exceeding the proposed tolerances.

IV. Toxicological Data Requirements (CFR 158.340)

A. Technical Sulfosate*:

Use Pattern: New chemical/Food and Feed Use

Last Updated: 07/27/92

		Required	Satisfied
81-1	Acute Oral Toxicity	yes	yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
81-7a	Acute Delayed Neurotox/hen	Yes+	No
81-7b	Acute Neurotoxicity/mammals	Yes#	No
82-1a	90-Day Oral (rodent)	Yes	Yes
82-1b	90-Day Oral (non-rodent)	Yes	Yes
82-5a	28-Day Neurotoxicity/hen	++	
82-5b	90-Day Neurotoxicity/mammal	Yes##	No
83-1a	Chronic Toxicity (rodent)Yes	Yes	
83-1b	Chronic Toxicity (non-rodent)	Yes	Yes
83-2a	Oncogenicity study (rat)	Yes	Yes
83-2b	Oncogenicity study (mouse)	Yes	Yes
83-3a	Teratology (rat)	Yes	Yes
83-3b	Teratology (rabbit)	Yes	Yes
83-4	2-generation Reproduction (rat)	Yes	Yes
84-2a	Mutagenicity - Gene Mutations	Yes	Yes
84-2b	Mutagenicity - Structural Chromosomal Aberrations	Yes	Yes
84-4	Mutagenicity - Other Genetic Effects	Yes	Yes
85-1	Metabolism	Yes	Yes

* The percent a.i. of technical grade sulfosate may vary from 19.2 to 62.0%, as a result of diluting the technical grade with the highest obtainable a.i. concentration (62%) in various amounts of water.

\+ Sulfosate is a salt composed of one fixed tertiary sulfur cation (trimethylsulfonium) and one phosphonate anion (carboxy-methylaminomethylphosphonate).

++ May be required if the acute delayed neurotoxicity study in hen (81-7) is positive.

\# Required for all new pesticides in the near future

Sulfosate has demonstrated neurotoxicity in acute oral, dermal and inhalation toxicity studies.

B. Formulation Touchdown 4LCE (39.8% ai):

Use Pattern: New chemical/Food and Feed Use

Last Updated: 07/27/92

		Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	No
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
82-2	21-Day Dermal	Yes	Yes

IV. TOXICOLOGICAL PROFILE

Updated 07/27/92

SULFOSATE TECHNICAL:

81-1	Acute Oral Toxicity in Rats. MRID 249802 STAUFFER CHEMICALS # T11185 November, 1982. Acceptable	LD_{50} = 748 mg/kg (males) LD_{50} = 755 mg/kg (females) Doses used: 500, 550, 600, 700, 800, and 900 mg/kg by gavage Signs: mild to severe depression, prostration, tremors, and slow/shallow respiration. Product tested: SC-0224 62% a.i. TOXICITY CATEGORY: 3
81-2	Acute Dermal Toxicity in Rabbits MRID 249802, 260508 Stauffer CHEMICALS # T-11185 November, 1982. Acceptable	LD_{50} > 2000 mg/kg (Both sexes; intact or abraded skin). Doses used: 800 -2200 mg/kg. Signs: Rabbits with abraded skin showed mild to severe depression at all doses levels and mild to moderate erythema. Rabbits with skin intact showed mild depression and mild erythema. Product tested: SC-0224 62% a.i. TOXICITY CATEGORY: 3
81-3	Acute inhalation toxicity in rats MRID 249802 Stauffer Chem No. T-11084 November, 1982 Acceptable	LC_{50} > 6.9 mg/L (both sexes, 4-hr, whole body exposure) Actual chamber concentration: 6.9 mg/L MMAD = 3.5 um at 64 min. 2.8 um at 184 min. SIGNS: wet fur, salivation, chromorhinorrhea Product tested: Sulfosate (62% a.i.) TOXICITY CATEGORY 3

6

INERT INGREDIENT INFORMATION IS NOT INCLUDED

81-3	Acute inhalation toxicity in rats MRID 412359-01 ICI No: CTL/P/2254 08/25/88 Unacceptable	LC_{50}> 5.18 mg/L (4-hr, nose only exposure) Actual chamber concentration: 2.65-6.3 mg/L MMAD: 4.56 ± 2.06 um [20% ≤ 2.5 um (inhalable) & 3.9% ≤ 1 um (respirable)] No mortality observed. SIGNS: (CNS & Autonomic) salivation, splayed gait, head & paw flicking, tail erection, shaking,subdue behavior, slow/deep breathing, decrease response to sound. Effects subsided on day 2. A limit test was not reached since only 3.9% of the aerolised sulfosate particles were of respirable size (EPA requires 25%). Product tested: Sulfosate 57.6% a.i. and [redacted] This study may be upgraded to acceptable when evidences are provided to show that optimum technology was used in generating the sulfosate containing aerosol. TOXICITY CATEGORY:
81-4	Primary Eye Irritation in Rabbits MRID 249802 STAUFFER CHEMICALS # T-11185 November, 1982. Acceptable	No effect on cornea. Effects on unwashed eyes: mild iritis (1/6 rabbits), and mild conjunctivitis (6/6 rabbits) at 24 hr (Draize score). All effects reversible by day 7. Effects on eyes washed after 20-30 sec. exposure: mild conjunctivitis (3/3 rabbits) lasting 3 days. Dose used: 0.1 ml SC-0224 62% a.i. TOXICITY CATEGORY: 3 (based on mild irritation of conjunctiva).

81-5	Primary Dermal Irritation in Rabbits MRID 249802 STAUFFER CHEMICALS # T-11185 November, 1982. Acceptable	24-hr exposure. Effects at 24 hr: intact and abraded skin showed mild erythema. Mild edema observed in 3/6 rabbits with skin abraded and 1/6 rabbits with skin intact. All dermal effects reversed within 72 hrs. Primary Irritation Score: 0.67. Dose used: 0.5 ml SC-0224 62% a.i. TOXICITY CATEGORY: 4
81-6	Dermal Sensitization in Guinea Pigs MRID 258398 Richmond Tox. Labs. # T-11269 October 12, 1984. Acceptable	SC-0224 Technical (56.3% a.i) is a mild skin sensitizer (Open Epicutaneous Test)
82-1(A)	Subchronic feeding rat MRID 412099-02 Stauffer Chem No. T-10888 4-3-87 Acceptable	NOELs: 800 ppm (MDT, 36 mg/kg/day) in males and 2000 ppm (HDT, 108 mg/kg/day) in females. LOEL: 2000 ppm (88 mg/kg/day) in males, based on a significant overall decrease in body weight gain (22% below controls). The HDT only caused sporadic and minimal decreases in body weight in females (secondary to a feed palability - related reduction in feed intake) and no significant overall decrease in B.W. gain. No significant changes were observed in clinical chemistry, hematology, urinalysis, organ weights, or macroscopic/microscopic histopathology. Doses tested: 0, 150, 350, 800, and 2000 ppm. MTD was reached for males only. Product tested: Sulfosate (19.2% a.i., 75.6% water)

8

82-1(b)	Subchronic feeding dog MRID 412099-02/03 Stauffer Chem No. T-11002 4-3-87 Acceptable	NOEL: 10 mg/kg/day (LDT) LOEL: 50 mg/kg/day (HDT) based on increase incidences and earlier onset of emesis and salivation. No changes in B.W., food consumption, clinical chemistry, hematology, urinalysis, organ weights, or macroscopic/microscopic histopathology were observed. Doses tested: 0, 10, 25, and 50 mg/kg/day by gavage. Dog's Strain: Beagle Product tested: Sulfosate (19.2% a.i., 75.6% water).
83-1a 83-2b	Feeding/Oncogenic (2-year) in Mice MRID 402140-06 412099-07 Stauffer Chem No. T-11813 4/3/87 Guideline	Oncogenic NOEL: >8000 ppm (HDT) Systemic NOEL: 1000 ppm (MDT) Systemic LOEL: 8000 ppm based on decreases in B.W. and feed consumption (both sexes), increases incidences of white matter degeneration in lumbar spinal cord (males only), and increase incidences of duodenal epithelial hyperplasia (females only). Doses used: 0, 100, 1000, and 8000 ppm Mice strain: Charles River Test material: Sulfosate 56.17% a.i.
83-1a 83-2a	Feeding/Oncogenic (2-year) in Rats MRID 402140-07 412099-05 Stauffer Chem No: T-11082 4/4/87 Guideline	Oncogenic NOEL: >1000 ppm (HDT) Systemic NOEL: 100 ppm (LDT) Systemic LOEL: 500 ppm (MDT) based on decreased levels of lactate dehydrogenase in males and females at 6 and 12 months. Effects at 1000 ppm: Decreases in B.W.(both sexes) and increase incidences of chronic laryngeal and nasopharyngeal inflammation (males). Doses used: 0, 100, 500, and 1000 ppm Rats strain: Charles River CrL:CD (SD)BR. Test material: Sulfosate 56.17% a.i.

9

83-1(b)	Chronic Feeding (1-year) in Dogs MRID 402140-05 Stauffer Chem. No: ECH T-11075 4/3/87 Minimum	Systemic NOEL: 10 mg/kg/day (MD) Systemic LOEL: 50 mg/kg/day (HD) based on decreases in LDH. Doses used: 0, 2, 10, and 50 mg/kg/day, by gavage. Selection of above dose range was based on (i) a 28-Day oral gavage study in which 150 mg/kg/day was lethal within 3 days and 75 mg/kg/day produced emesis, and (ii) a 90-Day study in which 50 mg/kg/day produced increase in emesis and salivation. Dog's Strain: Beagle Test material: Sulfosate 56.2% a.i.
83-3(a)	Teratogenicity in Rats MRID 249802 Stauffer Environ. Health Cen. No: T-11050 November 1982 Guideline	Terato.NOEL: >333 mg/kg/day (HDT) Fetotoxic NOEL: 100 mg/kg/day (MDT) Fetotoxic LOEL: 333 mg/kg/day based on significant decreases in B.W. Maternal NOEL: 100 mg/kg/day. Maternal LOEL: 333 mg/kg/day based on significant decreases in B.W. and feed intake. Effects at 333 mg/kg/day: Two deaths. Signs were significant increase in incidences of lethargy, salivation, and chromorhinorrhea. Doses used: 0, 30, 100, and 333 mg/kg/day by gavage to S-D rats. Test material: Sulfosate 19.2% a.i.
83-3(b)	Teratogenicity in Rabbits MRID 260966 Stauffer Chem. No: T-11052 6/21/83 Guideline	Developmental NOEL: >100 mg/kg/day (HDT). A/D ratio= 10/<100= <0.1. Maternal NOEL: <10 mg/kg/day (LDT) (Significant increase in incidences of diarrhea, head tilt, nasal discharge, wet stains on chin, red urine stain). Effects at 100 mg/kg/day: 38% mortality, 36% spontaneous abortion, significant decrease in feed intake, and in number of live fetuses per litter. Doses used: 0, 10, 40, and 100 mg/kg/day by gavage to Dla;(NZW)SPF rabbits. Test material: Sulfosate 56.2% a.i.

83-4	Reproduction (2-gen) in Rats MRID 258398 264429 Stauffer Chem. No: T-110-51 4/19/84 Guideline	Reproductive NOEL: >2000 ppm (HDT) Systemic NOEL: 150 ppm (LDT) Systemic LOEL: 800 ppm (MDT) based on reduced feed intake and B.W. in pups and parents, reduced absolute thymus weight (P1 M+F), increase platelet count (F2B adults, M+F). Doses used: 0, 150, 800, and 2000 ppm in Crl CD(SD)Br strain. Test material: sulfosate 19.2% a.i.
84-2(a)	Mutagenicity Reverse mut. (Ames Test) in Salmon. Typhi. MRID 249802 Stauffer Chem. No:T-10487 1/19/82 Acceptable	Not mutagenic at concentrations of 0.12, 0.37, 1.11, 3.33, and 10 mg/plate without S9, and of 0.56, 1.11, 1.67, 3.33, 5.0, 10, and 15 mg/plate with S9. Tester Bacteria: TA1535, TA1537, TA1538, TA98, and TA100 from Dr. Ames. Pos. controls: Na azide, 9-aminoacridine (9-AA), 2-nitrofluorene (2-NF), and 2-aminoanthracene (2-AA). Test material:sulfosate 90% a.i (estimated purity).
84-2(a)	Mutagenicity Reverse mut. (Ames Test) in Salmon. Typhi. MRID 260966 Stauffer Chem. No: T-12660 9/25/85 Acceptable	Not mutagenic at concentrations of 2.5, 5, 10, 20, and 40 ul/plate, with or without S9. Tester Bacteria: TA1535, TA1537, TA 98, and TA100. Pos. controls: Na azide, 9-AA, 2-NF. Cytotoxic Dose: HDT Test material: Sulfosate 55.6% a.i.
84-2(a)	Gene Mutation (SLRL) in Drosophila melanoga MRID 249802 Litton Bionetics No: 22169 6/13/82 Acceptable	Not mutagenic at doses of 25 and 50 mg/ml in "Sex linked recessive lethal test". Pos. control: EMS

84-2(a)	Gene Mutation (Forward Mut.) Mouse Lymphoma MRID 249802 Stauffer Chem T-10848 2/8/1982 Acceptable	Not mutagenic without S9. Significant reproducible increase in mutation frequency in presence of S9. Test medium pH not mentioned but was probably in the acid range. Indicator cells: L5178Y ($TK^{+}/^{-}$) mouse lymphoma cell line from Dr. Clive, RTP, No.Carolina). Concentrations used: 0.38, 0.75, 1.50, 3, 6, 8, 8.5, 9, and 10 mg/ml in presence of S9, and 0.38, 0.75, 1.5, 3, 6, 7, 8, 9, and 10 mg/ml w/o S9. Cytotoxic concentrations: >7 mg/ml
84-2(a)	Gene Mutation (forward mut.) Mouse Lymphoma MRID 260966 Stauffer Chem. No. T-12661 12/19/1985 Acceptable	Introduction of sulfosate in the test incubation medium reduced its pH to an acid range (5.67 -7.07). Under this experimental condition, sulfosate was positively mutagenic both in the presence of S9, at concentrations of 3-5 ul test material/ml, or without S9, at concentrations of 3.5 to 5ul/ml). When the pH of test incubation medium was readjusted to a physiological level of 7.4 (Addendum of 3/20,1987), concentrations from 5 to 10 ul/ml lost their mutagenic effect Indicator cells: L5178Y($TK^{+}/^{-}$) mouse lymphoma cell line (Dr. Clive, RTP, No.Carolina). Test material:Sulfosate 55.6% a.i. Cytotoxic concentrations: Unadjusted acidic medium: >5ul/ml pH adjusted medium: >7.75 ul/ml Pos. controls: N-Nitrosodimethyl-amine (DMN) with S9 and Ethyl-methanesulfonate (EMS) wo S9.
84-2(b)	Mutagenicity Cytogenetic Rat bone marrow MRID 249802 Stauffer Chem. No: T-10884 september 1982 Acceptable	Test animals: 6-wk old CD-Crl:CoBScd(SD)BR male rats. Not mutagenic (did not induce any structural chromosome aberrations in rats' bone marrow cells. Doses used: 21, 63, and 188 mg/kg (LD_{50}= 565 mg/kg). Test material: sulfosate 58.5% a.i. Pos. control: cyclophosphamide

84-2(b)	Mutagenicity (Micronucleus assay) Mouse bone marrow MRID 402140-04 412099-08 Stauffer Chem. No: EHC-T-12689 4/23/87 Acceptable	Test animals: Charles River D-1 str. Not mutagenic (did not induce any increase in the number of PCE containing micronuclei). Doses used: 700, 900, and 1100 mg/kg in males and 400, 600, and 800 mg/kg in females, based on results of a range finding study in which doses >1400 mg/kg killed 3/3 males within 48 hrs and doses >1000 mg/kg killed 2/3 females.
84-2(b)	Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-10875 7/6/1982 Acceptable	Positive mutagenicity (induces structural chromosomal aberration in CHO cells both in the absence of S9, at the concentration of 4 mg/ml, and in its presence, at concentrations of 10 and 12 mg/ml. Sister chromatid exchange (SCE) was not determined. Concentrations used: 2, 4, and 6 mg/ml w/o S9 and 2, 4, 6, 8, 10, and 12 mg/ml with S9. Test material: Sulfosate 58.5% a.i.
84-2(b)	Mutagenicity (Cytogenetic) in CHO cells MRID 249802 Stauffer Chem. No: T-11019 7/22/82 Acceptable	Positive mutagenicity (Induces structural chromosomal aberration in CHO cells both in the absence of S9, at concentrations of 6-8 ul/ml, and in its presence, at 1-8 ul/ml. No increase in SCE was observed. Concentrations used: 2, 4, 6, 8, 10, and 12 ul/ml. Test material: Sulfosate 72% a.i.
84-2(b)	Mutagenicity (cytogenetic) in CHO cells MRID 260966 Stauffer Chem. No: EHC T-12663 12/18/1985 Acceptable	pH of treatment medium was readjusted to 7.4-7.6 prior to testing. Not mutagenic (did not induce any structural chromosome abberrations in CHO cells or any increase in SCE) at concentrations of 4-10 ul/ml, with or w/o S9. Cytotoxic concentrations: None Pos. controls: Mitomycin C and Cyclophosphamide. Test material: sulfosate 55.6% a.i.

84-2(b)	Mutagenicity (cytogenetic) Mouse Lymphoma MRID 260966 Stauffer Chem. No: EHC T-12662 12/19/82 Acceptable	Indicator cells: L 5178Y ($TK^{+}/^{-}$) mouse lymphoma cell line from Dr. Clive, RTP, No.Carolina). Sulfosate concentrations of 5 ul/ml (w/o S9) and >3 ul/ml (w S9) induced chromosomal aberrations in the mouse lymphoma cells and increased the number of SCEs when the pH of the test medium was not readjusted (5.62-7.07). When the pH was readjusted to 7.4 concentrations from 4-10 ul/ml were not mutagenic. Cytotoxic concentrations: >5 ul/ml at acidic pH, and ≤ 10 ul/ml at physiological pH. Pos. controls: Ethyl methane-sulfonate & N-nitrosodimethylamine. Test material: 55.6% a.i.
84-4	Mutagenicity BALB/3T cells (morphological transformation) MRID 249802 Stauffer Chem. No: T-10849 1/4/82 Acceptable	Indicator cells: 1-1 subclone of clone A-31 of BALB/3T3 mouse cells from Dr. Kanunaga (NCI). Not mutagenic (did not induce an increase in the number of transformed foci) Concentrations used: 0.313, 0.625, 1.25, 2.5, and 5 mg/ml . Cytotoxic concentrations: >3 mg/ml Test material: sulfosate 90% estimated purity.

85-1	Metabolism in Rats MRID 258398 Stauffer Chem. PMS-148 2/4/85 Acceptable	Test material: (Methyl ^{14}C) trimethylsulfonium Carboxymethylaminomethylphosphonate) 96.5% purity, 20 mci/mmol. Identification of the (Methyl ^{14}C) trimethylsulfonium ion (^{14}C-TMS) in urine and fecal extracts done by TLC, GC/MS, autoradiography, and K iodoplatinate spray. After oral administration of 35 mg/kg (LDT) or 350 mg/kg (HDT) test material to S-D rats of both sexes, the ^{14}C-TMS ion is rapidly and almost completely absorbed from the GI tract and rapidly excreted unmetabolized mostly via the kidney. Urine recovery of ^{14}C (expressed as % of administered dose were: 80.8-95% at 24 hr and 91.4-98.5 at 120 hr. Most (95.3-97%) of the total radioactivity was unmetabolized ^{14}C-TMS ion. Fecal recovery of ^{14}C (expressed as % of administered dose were: 0.72-4.03% at 24 hr and 0.95-7.19% at 120 hr. All the radioactivity was unmetabolized ^{14}C-TMS ion. $^{14}CO_2$ in expired air was negligible. Tissues residues were negligible: 0-0.148 (LD) and 0-10.6 ppm (HD) sulfosate equivalents. The lack of metabolism may be explained by the hydrophilic nature of TMS ion. Acute toxic effects at the HDT: lethargy, ataxia, slow/labored breathing, salivation, occasional tremors. Signs lessened after 24 hrs.

85-1	Metabolism in Rats MRID 412359-03 ICI Americas Inc. No: T-12906 12/20/88 Acceptable	Test material: Trimethylsulfonium Carboxymethylaminomethylphosphonate ^{14}C-radiolabeled on the anionic moity (Carboxymethylaminomethyl-phosphonate), 93.2% radiopurity, 9.8 mCi/mmol. Identification of anion by TLC, autoradiograhy, and GC/MS. Males and females S-D rats iv-treated with 25 mg/kg (LDT) test material excreted 90% of the administered dose in urine. After oral administration of the LDT or the HDT (250 mg/kg), the test material was rapidly excreted in urine and feces (70-82% of the total radioactivity administered was excreted within 24 hrs, and 85-94% within 120 hrs). Absorption was incomplete: only 47-57% of total radioactivity was recovered in urine. Fecal excretion was 36-42% of the administered dose. Most of the recovered radioactivity was unmetabolized carboxymethyl-aminomethylphosphonate (80-90% of urine and 77-96% of feces total radioactivity).One fecal metabolite was aminomethylphoshonic acid (8.5% of total fecal radioactivity in female rats dosed repeatedly (14 single daily LD of unlabeled test material followed by a single LD of labeled test material. $_{14}CO_2$ in expired air was negligible. Combined tissue residues were only $\geq$0.32% of administered dose. Carcasses contained 2.25% of the administered dose, most of it located in bones. Acute toxic signs observed with the HD: lethargy, moderate/severe depression, tremors, dehydration, and reduced feed consumption. Signs lasted 72 hours.

16

IV. TOXICOLOGICAL PROFILE

Updated 3/05/91

FORMULATION TOUCHDOWN 4LCE (39.8% a.i.):

81-1	Acute Oral Toxicity in Rats. MRID 408938-02 STAUFFER CHEMICALS # T12589 2/12, 1987. Acceptable	LD_{50} = 1760 mg/kg (males) LD_{50} = 1298 mg/kg (females) SIGNS: depression, hypersensitivity to touch and sound. NECROPSY: dark livers, spleens, and/or lungs, and test-like material in GI tract. TOXICITY CATEGORY: 3
81-2	Acute Dermal Toxicity in Rabbits MRID 408938-02 Stauffer CHEMICALS # T-12589 November, 1987. Acceptable	LD_{50}> 2000 mg/kg (Both sexes) SIGNS: mild depression and diarrhea. TOXICITY CATEGORY: 3
81-3	Acute inhalation toxicity in rats MRID 408938-03 Stauffer Chem No. T-12983 6/22/1987 Unacceptable	A respirable aerosol could not be generated: the test material was highly viscous and formed excessive foam. Registrant was advised to pursue additional testing. Ways to reduce foaming were suggested (Dilute test material, reduce surfactants) as well as ways to improve particulation (form dense fog and run through a cyclone separator to remove large particles). TOXICITY CATEGORY: Not classified

17

81-4	Primary Eye Irritation in Rabbits MRID 408938-02 STAUFFER CHEMICALS # T-12589 2/12/1987. Acceptable	Unwashed eyes: Moderate iritis, and mild to moderate conjunctival irritation. Effects cleared by day 7. Eyes washed: (Exposure of 20-30 sec.) Mild to moderate conjunctival irritation. Dose: 0.1 ml (pH of test material= 5.85). TOXICITY CATEGORY: 3
81-5	Primary Dermal Irritation in Rabbits MRID 408398-02 STAUFFER CHEMICALS # T-12589 2/12/1987 Acceptable	Non-irritating (4-hr exposure) TOXICITY CATEGORY: 4
81-6	Dermal Sensitization in Guinea Pigs MRID 408398-04 Stauffer Chem. No.T-12588 8/4/1987 Acceptable	Not a skin sensitizer (Modified Buehler test).
82-2	21-Day Dermal in Rats MRID 412099-04 Ciba-Geigy Corp. No: CTL/P/2496, LR0535 7/7/89 Acceptable	Doses: 25, 250, 1000 mg/kg/day (6hr/day/21 days) in 0.0021, 0.0027, and 0.0826 ml/100 g B.W. NOEL= 250 mg/kg (MDT) EFFECTS: dermal irritation in HDT males (dermal histology was normal). Slight increase in testes weight at 25 and 1000 mg/kg/day with normal histology. Occasional sciatic nerve fiber degeneration (1 male and 2 fem. out of a total of 10) at 1000 mg/kg/day.

18

V. Data Gaps:

A. With Tech. Sulfosate:

(1) Acute delayed Neurotoxicity/hen (81-7a): Sulfosate (formerly SC-0224) is a salt composed of a fixed tertiary sulfur cation (trimethylsulfonium) and a phosphonate anion (carboxymethylaminomethyl-phosphonate). Phosphonate containing OPs are known to cause acute delayed neurotoxicity (DS Barrett & al in "A Review of organophosphorus ester-induced delayed neurotoxicity", Vet. Hum. Toxicol., 27, (1), feb. 1987.

2. Acute Neurotoxicity/mammals (81-7b): This test will be required to support the registration of pesticides in the near future. It is presently required for sulfosate because this compound has demonstrated general neurotoxic symptoms in acute oral, dermal, and inhalation toxicity studies.

3. 90-Day Neurotoxicity/mammals (82-5b): Sulfosate has demonstrated neurotoxicity in acute oral, dermal and acute toxicity studies (MRIDs 249802, 260508, 412359-01)

4. Acute Inhalation toxicity study (81-3) with Touchdown 4LCE.

5. In addition, TB will require a 28-Day Neurotoxicity/hen (82-5a) if the acute delayed Neurotoxicity/hen is positive.

B. With The Formulation Touchdown 4LCE:

An acute Inhalation toxicity study is required.

VI. Action Taken to Obtain Additional Information or Clarification:

RD has been notified of the Data Gaps cited above.

VII. Established Tolerances:

There are no existing tolerances for the pesticide sulfosate (trimethylsulfonium carboxymethylaminomethylphosphonate, formerly SC-0024). Tolerances are however established for glyphosate (iso-propylamine salt of carboxymethylamino-methylphosphonate), a pesticide closely related in chemical structure to sulfosate (40 CFR 180.364).

VIII. Reference Dose (RfD):

There are no defined RfD for sulfosate.

19

IX. Pending Regulatory Actions:

HED is not aware of any pending regulatory action against the registration of this pesticide.

X. Toxicological Issues Pertinent to Granting this Request:

A. Sulfosate's potential for neurotoxicity is of concern. The following neurotoxic symptoms were observed in acute oral, dermal, or inhalation studies with both the technical product and the formulation:

(1) Ataxia, tremors, mild to severe depression, prostration (oral route, tech. product, MRID 249802) and depression, ataxia, prostration, tremors (oral route, 4LC, MRID 249803) in rats.

(2) Mild to severe depression (dermal route,, tech. sulfosate, MRID 249802 & 260508) and mild to severe depression, prostration, and tremors (dermal route, 4LC, MRID 249803) in rabbits.

(3) Splayed gait, head and paw flicking, shaking, subdued behavior, decrease response to sound (inha. route, tech. sulfosate, MRID 412359-01) and reduced activity, prostration (inha. route, 4LC, MRID 258398) in rats.

C. The following neurohistopatology were also observed in subchronic and chronic/oncogenicity studies:

(1) White matter degeneration of the lumbar spinal cord of male mice (oncogenic study, MRID 402140-06 & 412099-07).

(2) Sciatic nerve degeneration (21-Day dermal, 4LCE, MRID 412099-04).

Organophosphorus Compounds are known to cause neurotoxicity. Sulfosate is a organophosphonate. Several pesticides belonging to this group of chemicals are also known to cause acute delayed neurotoxicity in the hen and in humans.

B. In some of the in-vitro mutagenicity tests conducted in 1982, Sulfosate induced a false positive mutagenic effect. These studies included MRID 249802, studies Nos. T-10848 (Forward mutation/Mouse Lymphoma cells), T-10875 (Structural Chromosomal Abberrations/CHO cells) and T-11019 (Structural Chromosomal Abberrations/CHO cells). A common feature of these tests was that the pHs of the test incubation media were acidic (pH 5.67 -7.07) due to the addition of sulfosate. These positive results were no longer observed [see MRID 260966, studies Nos. T-12661 (Forward Mutation/Mouse Lymphoma cells), T-12662 (Structural

20

Chromosomal Abberrations/CHO cells), and T-12663 (Structural Chromosomal Abberrations/Mouse Lymphoma cells)] when the pH was readjusted to a more physiological level (7.4) before the conduct of the mutagenicity test.

C. Composition of Technical Grade Sulfosate

Technical sulfosate is usually supplied as an aqueous solution containing about 52% active ingredinet. The very viscous nature of sulfosate precludes the practical manufacture of a technical grade with a standard a.i. content (sulfosate forms an intractable glass-like product if its water content is ≤ 30%). The various "technical grade sulfosates" used in the toxicological studies described under "Toxicological Profile" above are either an aqueous sulfosate concentrate containing 62% ai or aqueous dilutions of this concentrate to ai concentrations of 19.2, 52, and 56.17%.

XI. Relevant Consideration in setting the tolerance:

The dietary impact of the requested tolerances is addressed by the Tolerance Support Chemistry Branch (TSCB). See response to data package No. D153710.

24